

Alpha 2 delta ($\alpha_2\delta$) ligands, gabapentin and pregabalin: what is the evidence for potential use of these ligands in irritable bowel syndrome

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Irritable bowel syndrome (IBS) is a complex disorder that is characterized by abdominal pain and altered bowel habit, and often associates with other gastrointestinal symptoms such as feelings of incomplete bowel movement and abdominal bloating, and extra-intestinal symptoms such as headache, dyspareunia, heartburn, muscle pain, and back pain. It also frequently coexists with conditions that may also involve central sensitization processes, such as fibromyalgia, irritable bladder disorder, and chronic cough. This review examines the evidence to date on gabapentin and pregabalin which may support further and continued research and development of the $\alpha_2\delta$ ligands in disorders characterized by visceral hypersensitivity, such as IBS. The distribution of the $\alpha_2\delta$ subunit of the voltage-gated calcium channel, possible mechanisms of action, pre-clinical data which supports an effect on motor-sensory mechanisms and clinical evidence that points to potential benefits in patients with IBS will be discussed.

Keywords: $\alpha_2\delta$ ligands, gabapentin, pregabalin, irritable bowel syndrome, visceral sensitivity, central sensitization, peripheral sensitization, motility

INTRODUCTION

ABDOMINAL PAIN AND VISCERAL HYPERSENSITIVITY

Abdominal pain and discomfort along with altered bowel habit are integral to the diagnosis of irritable bowel syndrome (IBS). Although disordered bowel habit can often be improved in these patients, efficacious treatment of pain, abdominal discomfort, and associated symptoms, such as bloating, remains challenging. The identification and development of new drugs to treat these symptoms has been largely unsuccessful and remains problematic, probably linked to the complexity of the functional gastrointestinal disorders (FGIDs) in which multiple factors appear to contribute to their equally multifarious pathophysiology. For example, genetic predisposition, infection, and traumatic events in early life may all predispose individuals to developing IBS, whilst chronic stress, psychological symptoms, and maladaptive coping mechanisms can increase the frequency and severity of symptoms (Levy et al., 2006; Chitkara et al., 2008; Saito and Talley, 2008; Spiller and Garsed, 2009). Pathophysiologies identified to date include gastrointestinal dysmotility, abnormalities in the inflammatory/immune system, increased intestinal permeability, unstable or altered enteric flora, psychopathology, visceral and somatic hypersensitivity, and abnormal CNS processing (Longstreth et al., 2006; Spiller et al., 2007). Although not all abnormalities are present in all patients, visceral hypersensitivity which often associates with the symptoms of pain (Posserud et al., 2007) and bloating (Posserud et al., 2007; Agrawal et al., 2008) and which is often exacerbated by stress, is thought by many to be a determinant or biological measure of IBS (Mertz et al., 1995; Bouin et al., 2002).

For example, Mertz et al. (1995) showed altered rectal perception in almost all IBS patients in the form of either lowered sensory thresholds, increased sensation intensity or altered viscerosomatic referral, whilst Bouin et al. (2002) suggested that a pain threshold of less than 40 mmHg in the rectum correctly identified IBS from non-IBS subjects. In addition, whilst only approximately half of IBS patients appear to exhibit lowered rectal sensory thresholds to balloon distension (Whitehead and Palsson, 1998; Posserud et al., 2007), almost all patients (70%) show hypersensitivity elsewhere in the gastrointestinal tract, especially in the jejunum (Francis et al., 1995; Hammonds et al., 1998). Moreover, in the latter studies (Francis et al., 1995; Hammonds et al., 1998) within the group as a whole, and especially in those subjects with diarrhea, lower pain thresholds were observed throughout the entire GI tract compared with healthy controls.

CENTRAL SENSITIZATION

These observations of pan-gastrointestinal visceral hypersensitivity and increased viscerosomatic referral, along with reported increases in expression of extra-intestinal symptoms such as headache, dyspareunia, heartburn, muscle pain and back pain (Whorwell et al., 1986; Mayer and Gebhart, 1994), and presence of fibromyalgia in some patients (Whitehead et al., 2002; Almansa et al., 2009) are consistent with a widespread aberrant central processing of pain (central sensitization) in these patients. Further support is provided by the observations that whilst healthy volunteers exhibit an inhibition of the somatic nociceptor flexion reflex (R-III) to slow ramp distension of the rectum, IBS

patients exhibit a facilitation of this reflex, suggesting enhanced spinal processing in IBS (Coffin et al., 2004). In addition, there are an increasing number of studies suggesting that IBS patients may also be hypersensitive to somatic stimuli. One such study, showed hypersensitivity to rectal balloon distension and cutaneous thermal stimulation of the hand and foot in IBS compared with control subjects (Verne et al., 2001). Interestingly foot hypersensitivity was greater than hand hypersensitivity, suggesting greater convergence and overlap of rectal and foot afferents at common lumbosacral levels (greater central hyperalgesia) than rectal and hand afferents at the levels of the cervical spinal (Verne et al., 2001).

POSSIBLE SYNERGISTIC MECHANISMS

Along with the spinal (central) sensitization, other possible synergistic mechanisms of visceral hypersensitivity include disturbances in the cognitive and emotional aspects of pain (e.g., hypervigilance, somatization, catastrophizing, depression), alterations in descending excitatory and inhibitory pathways (e.g., diffuse noxious inhibitory control, DNIC), and sensitization of afferent nerves (e.g., peripheral sensitization due to for example mucosal insult). A quantitative meta-analysis of functional neuroimaging studies in IBS patients during rectal distension showed greater recruitment of attentional (lateral prefrontal cortex), affective (ventral anterior cingulate cortex [ACC], amygdala, dorsal pons), and homeostatic afferent circuits (insula, dorsal ACC, thalamus) compared with controls, with increased regional activity in the insula (INS) and anterior midcingulate cortex (amMCC) being most commonly reported (Labus et al., 2009). More recent studies investigating anatomical differences in the brain between IBS and control subjects have shown morphometric changes in gray matter density predominantly in areas involved in cognition and evaluation, with changes in other areas of the brain being generally explained by anxiety and depression levels in the IBS patients (Seminowicz et al., 2010). In another study by Heymen et al. (2010), in which DNIC was assessed in IBS compared with healthy subjects by measuring the reduction in left hand thermal pain intensity during counter irritation by submersion of the right hand in 12°C water (conditioning stimulus, CS), and controlling for the non-specific effects on pain perception, such as distraction from the CS, psychological symptoms, and cardiovascular reactivity, it was shown that IBS patients demonstrate deficient DNIC probably attributed to disordered central analgesic mechanisms. This deficit has subsequently been shown to directly correlate with visceral hypersensitivity (Piche et al., 2010). Indeed in the morphological study described above significant reductions in gray matter density were observed in the periaqueductal gray, an area known to play a major role in descending pain modulation, which was independent of anxiety and depression (Seminowicz et al., 2010). Other studies have shown that peripheral mucosal insults, such as the presence of inflammation, injury or excess acid do not only increase pain sensitivity at the site of injury (primary hyperalgesia/peripheral sensitization) but also at more remote sites in the gastrointestinal tract (secondary hyperalgesia), via the process of central sensitization (Anand et al., 2007; Knowles and Aziz, 2009). One example in FGIDs, is the observation that pain thresholds to electrical stimulation were not just reduced at the distal end of the esophagus where acid was infused but also in the unexposed

proximal esophagus of patients with non-cardiac chest pain, with this sensitization process being significantly magnified and prolonged compared with healthy volunteers (Sarkar et al., 2000). Another possible example is the onset of IBS following GI infection (post-infectious IBS) where persistent sensitization of the primary afferents due to for example increased mast cells numbers, T lymphocytes, and expression interleukin (IL)-1 β (peripheral sensitization), especially in the presence of risk factors such as depression, hypochondriasis, and adverse life events (Spiller and Garsed, 2009), could lead to central sensitization and the persistence of symptoms, allodynia (pain to a stimulus that does not normally provoke pain), hyperalgesia (increase in intensity of pain to a stimulus that normally provokes pain), and dysmotility long after the resolution of illness.

Thus there appears to be a dyssynergy between the interaction of peripheral and central pain mechanisms, along with influences from cognitive and emotional factors, and abnormalities in descending inhibitory pathways that may all lead to the sensation of abdominal pain and hypersensitivity in IBS. Central mechanisms perhaps play a pivotal role integrating between these processes and thus may represent a promising target for the development of drugs for the treatment of IBS. For a more detailed discussion of central, peripheral, and psychological processes in IBS see the reviews Van Oudenhoove and Aziz (2009), Knowles and Aziz (2009), and Anand et al. (2007).

$\alpha_2\delta$ BINDING SITES

Gabapentin (Neurontin) was first introduced as an antiepileptic drug but has more recently been used in the treatment of postherpetic neuralgia, diabetic neuropathy, migraine prophylaxis, and chronic pain conditions (Taylor, 2009; Tzellos et al., 2010). Pregabalin (Lyrica) is a second-generation compound structurally related to gabapentin and approved in the US for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and as adjunctive therapy for adults with partial onset seizures and for generalized anxiety disorder (GAD). In Europe pregabalin is approved for the treatment of neuropathic pain, epilepsy, and generalized anxiety disorder (Taylor, 2009; Tzellos et al., 2010). It has been, or is being, assessed in many clinical trials for disorders such as IBS and neuropathic pain in acute spinal cord injury (see US National Institute of Health, www.ClinicalTrials.gov). Pregabalin has been shown to be 2–10 times more potent than gabapentin and to possess more linear pharmacokinetics (Ben-Menachem, 2004; Huckle, 2004; Taylor, 2009; Tzellos et al., 2010).

Although structurally related to γ -aminobutyric acid (GABA), a major inhibitory neurotransmitter in the CNS, gabapentin, and pregabalin are functionally inactive at GABA_A, GABA_B, or benzodiazepine receptors, and are not converted metabolically into GABA or a GABA receptor agonist (Ben-Menachem, 2004; Huckle, 2004; Taylor, 2009; Tzellos et al., 2010). In addition, clinically effective concentrations of gabapentin and pregabalin have been shown to have no effect on GABA synthesis, uptake or degradation (Ben-Menachem, 2004; Huckle, 2004; Field et al., 2006; Taylor, 2009; Tzellos et al., 2010).

Both gabapentin and pregabalin bind with high affinity to $\alpha_2\delta$ subunits of voltage-gated calcium channels and this has been

proposed as a likely site of their action. Further, in mice with mutations of the $\alpha_2\delta$ subunits that prevent drug binding, pregabalin and gabapentin are devoid of analgesic and anticonvulsant activity (Field et al., 2006). Voltage-gated calcium channels are ubiquitous in the body and are made up of an α_1 subunit, which makes up the ion-conducting pore, coupled together with other subunits including β , γ , and $\alpha_2\delta$. There is great heterogeneity within the family of α_1 subunits, of which 10 members have been described in mammals (for review; Catterall et al., 2005). The $\alpha_2\delta$ subunit appears to play a role not only in the operational characteristics of individual channels, but also to enhance trafficking of the α_1 subunits to the cell membrane, so influencing the number of functional calcium channels (Hendrich et al., 2008; Mich and Horne, 2008). The $\alpha_2\delta$ subunit exists as four distinct subtypes and these are encoded by four distinct genes (Klugbauer et al., 1999; Qin et al., 2002). Only subtypes 1 and 2 have been shown to exhibit binding for gabapentin and pregabalin and therefore might be expected to underwrite the analgesic, anticonvulsant, and anxiolytic activity of these drugs (Gong et al., 2001; Qin et al., 2002).

Despite the widespread localization of voltage-gated calcium channels, the focus of studies to map the distribution of the $\alpha_2\delta$ subunit has largely been restricted to tissues of the central nervous system, with few studies exploring the potential for wider distribution. At both the mRNA and protein level, $\alpha_2\delta$ -subtype 1 is widely distributed throughout human brain (Gong et al., 2001). This widespread distribution of mRNA for the $\alpha_2\delta$ -subtype 1 has been confirmed in the central nervous system of the rat and was reported in regions of the CNS involved in cortical processing, learning and memory, defensive behavior, neuroendocrine secretion, autonomic activation, primary sensory transmission, and general arousal (Cole et al., 2005). These observations have been confirmed at the protein level using immunostaining with an antibody specific for $\alpha_2\delta$ -subtype 1 (Taylor and Garrido, 2008). In this study, the most prominently stained regions of the CNS included those areas involved in pain signaling, including the amygdala, entorhinal cortex, hippocampus, ACC, and insula (Taylor and Garrido, 2008). In addition, a population of small diameter peripheral sensory neurones in the dorsal root ganglia, together with their projections to the spinal cord, stained prominently (Taylor and Garrido, 2008). Immunostaining in the GI tract was also investigated, although only data from the small intestine was reported showing moderate staining in the smooth muscle (Taylor and Garrido, 2008). To date, there has been only one report of neuronal $\alpha_2\delta$ subunit expression in the intestine. In the guinea-pig, *in situ* hybridization has revealed the $\alpha_2\delta$ -subtype 1 localized on the intrinsic primary afferent neurones of the intestine, where they appear to be associated with N-type calcium channels (Needham et al., 2010). In these neurones, pregabalin had inhibitory effects on both the action potential and the after hyperpolarization, raising the possibility that pregabalin may be able to reduce the excitability of these sensory neurones and so potentially inhibit GI hypersensitivity by an effect at these sites. The distribution of $\alpha_2\delta$ -subtype 2 has been less extensively characterized. However, in the rat, mRNA encoding $\alpha_2\delta$ -subtype 2 has been shown to be widely distributed within the CNS, with particularly dense staining in the brainstem, the periaqueductal gray matter, the spinal cord, and dorsal root ganglia (Cole et al., 2005). These are regions

known to play an important role in autonomic function and pain processing. In tissues from human, mRNA for $\alpha_2\delta$ -subtype 2 was detected in several brain regions but not in colon or small intestine (Gong et al., 2001). The absence of $\alpha_2\delta$ -subtype 2 in human jejunum was also confirmed at the protein level.

The functional consequences of the binding of gabapentin/pregabalin with the $\alpha_2\delta$ protein remain controversial. Data from recombinant systems suggests that the function of the $\alpha_2\delta$ subunit is heavily dependent on the subtype of α_1 protein with which the $\alpha_2\delta$ subunit is co-expressed and the cell system into which the proteins are engineered. However, it is widely accepted that the mechanism of action of these agents involves a modulation of calcium conductance, but the precise mechanism for this remains to be elucidated. The modulation of calcium currents by gabapentin has been demonstrated in several studies of isolated neurones (Stefani et al., 1998; Sutton et al., 2002; van Hooft et al., 2002), although other studies have struggled to demonstrate such an effect (Schlicker et al., 1985). More recently, it has been proposed that gabapentin may exert an action through binding to the $\alpha_2\delta$ subunit within the cytosol, rather than at the cell surface, and that this interaction can over time reduce the trafficking of $\alpha_1/\alpha_2\delta$ complexes to functional sites within the cell membrane (Hendrich et al., 2008; Mich and Horne, 2008). Thus gabapentin and pregabalin may exert a range of effects, either acute or chronic, mediated through diverse mechanisms, to modulate calcium flux in nerve terminals. The consequences of this disruption of calcium-mediated membrane depolarization have been investigated extensively. Both gabapentin and pregabalin have been shown to inhibit the release of a wide range of neurotransmitters including noradrenaline, dopamine, 5-HT, acetylcholine, glutamate, substance P, and CGRP from isolated slices of brain and spinal cord from several species following stimulation with either potassium or capsaicin (Dooley et al., 2000; Patel et al., 2000; Fehrenbacher et al., 2003; Brawek et al., 2008). However, the inhibitory effect of gabapentin and pregabalin may be stimulus-dependant, as illustrated in the neocortex, where the magnitude of inhibition of the release of noradrenaline was reduced when neurotransmitter release was evoked by electrical stimulation rather than potassium (Dooley et al., 2000). It has been suggested that $\alpha_2\delta$ ligands may only exert their inhibitory effects on neurotransmitter release in "sensitized" situations and may exert only limited effects in situations of normal physiology. For example, in the spinal cord, gabapentin was only able to exert its presynaptic inhibitory influence on postsynaptic currents in animals in which experimental diabetic neuropathy had been established with streptozotocin and not in unsensitized animals (Patel et al., 2000). Similarly, the pregabalin-mediated reductions in substance P and CGRP release in the spinal cord of the rat are manifest only in animals in which inflammation had been induced following pre-treatment with intraplantar Freund's adjuvant and are absent in untreated animals (Fehrenbacher et al., 2003).

More recently, an additional mechanism of action has been suggested for gabapentin and pregabalin. In cell or neuronal cultures gabapentin and pregabalin were shown to inhibit the activation of the transcription factor NF- κ B evoked by substance P (Park et al., 2008). If confirmed in additional studies, these observations might help explain the increased efficacy of gabapentin and pregabalin

in circumstances of prior inflammation or sensitization, which might be expected to lead to up-regulation of the NF- κ B signaling pathway.

PRE-CLINICAL MODELS OF NON-GI NEUROPATHIC PAIN

The anti-allodynic and anti-hyperalgesic properties of gabapentin and pregabalin have been established in a wide range of animal models and the literature is too extensive to review here. In summary, both of these $\alpha_2\delta$ ligands have been shown to manifest these properties in animal models of inflammatory, surgical, and neuropathic pain, including the inhibition of both the static and dynamic components of allodynia (for example; Field et al., 1997a,b, 1999). Interestingly, in a study of both sympathetically-maintained and sympathetically-independent neuropathic pain, pregabalin was particularly potent at inhibiting both tactile and cold allodynia when given by the intrathecal route, suggesting a predominantly spinal site of action, although the involvement of supraspinal centers cannot be ruled out (Han et al., 2007). Pregabalin was unable to inhibit cold allodynia in the model of sympathetically-independent neuropathic pain when given via the intraperitoneal route (Han et al., 2007). Experiments involving direct recording from spinal neurons have demonstrated the ability of pregabalin to inhibit the C-fiber mediated response of spinal nociceptive-specific neurons, without any effect on the responsiveness of A- δ fibers (You et al., 2009). Further, pregabalin was also able to inhibit central sensitization of the spinal neurons induced by application of bee venom. Spinal transection confirmed that the effect of pregabalin in this study was likely to involve supraspinal centers, mediated through descending inhibitory controls (You et al., 2009).

PRE-CLINICAL MODELS OF GI SENSATION AND MOTILITY

Following the demonstration of the efficacy of gabapentin and pregabalin in animal models of neuropathic pain, investigations of the profile of these agents in small animal models of visceral pain followed. Initial focus was on understanding whether gabapentin and pregabalin might have utility in the treatment of IBS and so studies focused on models of rectal or colonic hypersensitivity. Caution needs to be applied when interpreting these data given the recent history of notable failure of these models to predict the effects of other new drugs on human pain and discomfort (e.g., those acting at neurokinin-1, NK₁, or corticotrophin releasing factor-1, CRF₁, receptors). Despite this in the rat, the intraperitoneal administration of lipopolysaccharide (LPS) results, some 9–12 h later, in hypersensitivity of the rectum. The hypersensitivity can be demonstrated following rectal distension with a small balloon and is manifest as both allodynia as well as hyperalgesia. In this model, pregabalin, following either oral or intraperitoneal administration, suppressed the rectal hypersensitivity response to LPS (Eutamene et al., 2000). Pregabalin (1–30 mg/kg p.o.) dose-dependently inhibited the allodynia observed following distension with the lowest volume of 0.4 mL. However, only the 10 mg/kg dose was able to reduce the nociceptive effect of the larger volumes of distension. These observations were then extended in a more chronic model of colonic allodynia (Diop et al., 2002). Seven days after the administration of trinitrobenzene sulfonic acid (TNBS) into the proximal colon of the rat, an allodynia to distension

was demonstrated in the distal colon of the animal. Histological analysis revealed an inflammatory response in the proximal colon, characterized by the presence of inflammatory cells, necrosis, and hyperemia, 3 days after dosing with TNBS. This response had substantially diminished by day 7 and in the distal colon, no increase in inflammatory cells was observed at any time point. Hyperemia appeared to persist to day 7, the study day for these experiments. Pregabalin (30–200 mg/kg s.c.), given 30 min prior to the balloon distension of the distal colon, dose-dependently reversed the allodynia observed 7 days after TNBS administration. Similar effects were seen following oral administration, 1 h prior to balloon distension. In control animals not pre-treated with TNBS, the highest dose of pregabalin (200 mg/kg s.c.), which fully reversed TNBS-induced allodynia, had no effect on colonic pain thresholds, in contrast to morphine (0.3 and 1.0 mg/kg) which significantly raised thresholds (Diop et al., 2002). In this model, the inflammatory stimulus in the proximal colon establishes a secondary hyperalgesia and allodynia in the distal colon, presumably through central sensitization at the level of the lumbar spinal cord, although possibly also involving higher centers. These central nervous system structures are the likely site of action of pregabalin in this model and in the absence of sensitization, pregabalin had no effect on sensation.

A series of studies with the prototype $\alpha_2\delta$ ligand gabapentin, confirmed that the effects on visceral pain were shared across the class and not restricted to pregabalin. In both mice and rats, gabapentin was shown to reduce the response evoked by intraperitoneal administration of acetic acid, a model of acute visceral pain. Gabapentin (50–200 mg/kg i.p.), dose-dependently inhibited the number of abdominal contractions evoked by intraperitoneal acetic acid when given 40 min ahead of the stimulus (Feng et al., 2003). The maximum effect was seen at 200 mg/kg and inhibited the abdominal response by approximately 75%. This dose of gabapentin impaired the performance of rats on the beam-balance test, suggestive of sedation, which can interfere with the interpretation of tests of analgesia, raising the possibility that the antinociceptive effect of gabapentin was secondary to sedative effects. In this study, the investigators also attempted to develop some mechanistic understanding of these observations and measured acute changes (over a 90-min observation) in the intrathecal levels of several amino acids. Intraperitoneal administration of acetic acid evoked large rises in both aspartate and glutamate. These increases were inhibited completely by prior administration of gabapentin (100 mg/kg i.p.). In addition, acetic acid also increased the intrathecal levels of the inhibitory amino acid serine, an increase that was also inhibited by gabapentin pre-treatment. Intrathecal levels of the inhibitory amino acid, glycine was reduced to below baseline levels by gabapentin. In a broadly similar study, this time conducted in mice, Stepanovic-Petrovic et al. (2008) confirmed the activity of gabapentin to inhibit the nociceptive effects of peritoneal irritation evoked by acetic acid. In this study, intraperitoneal administration evoked a writhing response, characterized by abdominal contractions coupled with elongation of the body and extension of the hindlimbs. Intraperitoneal administration of gabapentin (10–70 mg/kg), 1 h before the acetic acid, dose-dependently inhibited the writhing response. Once again, this group compared the potency of gabapentin to inhibit

acetic-acid-induced writhing with its ability to impair motor function, assessed using the rotarod test (a test of performance in which the rodent is placed on a suspended horizontal rotating rod [not high enough to injure the animal but high enough that the animal avoids falling off] to measure balance, coordination and motor planning). In this study, gabapentin was devoid of activity in the rotarod test, even at doses of 2000 mg/kg, thus making it unlikely that the observed antinociceptive effects were occurring secondary to sedation. In an interesting study from Meymandi and Sepehri (2008), the antinociceptive effect of gabapentin (1–100 mg/kg i.p.) was confirmed in the acetic acid-induced writhing model. In the same study, the dose-response curve to morphine was also constructed and then a low effective dose of gabapentin was given as a combination with a sub-therapeutic dose (0.25 mg/kg i.p.) of morphine. This combination produced a synergistic effect, as writhing was inhibited by over 90% compared to control levels. Similarly, when the sub-therapeutic dose of morphine was combined with a sub-therapeutic dose of gabapentin (10 mg/kg i.p.), a synergistic response was observed, with writhing inhibited by approximately 70%. Interestingly, these synergistic effects were not inhibited by treatment with naloxone. Similar observations, of a synergistic interaction between gabapentin and morphine in models of visceral pain have been made previously in a rat model of experimental pancreatitis induced by bradykinin infusion into the pancreas (Smiley et al., 2004). In this model, gabapentin (100–300 μ g intrathecally) only modestly inhibited the behavioral response to bradykinin. However, when the 300 μ g intrathecal dose of gabapentin was combined with low intrathecal doses of morphine, shown previously to have modest if any inhibitory effects in this model, significant inhibition of all aspects of the behavioral response to bradykinin was observed. These observations taken together illustrate the inhibitory effect of gabapentin on visceral pain, strongly support the concept that this effect is not underwritten or confounded by inhibiting arousal and point to potential synergy with other antinociceptive mechanisms. These data also provide *in vivo* evidence to support the hypothesis that gabapentin reduces the release of excitatory and inhibitory neurotransmitters in the spinal cord.

Recently, a study has been published comparing the effect of pregabalin in the TNBS model of acute hypersensitivity with a model of acute hypersensitivity induced by restraint stress (Ohashi-Doi et al., 2010). As one might predict from previous data, pregabalin (10–100 mg/kg p.o.) reduced colonic nociceptive thresholds dose-dependently in animals sensitized previously with TNBS. In the stress restraint model, increased fecal output in terms of number of pellets and fecal weight was observed during the period of restraint stress. Pregabalin, over the same dose range as examined in the TNBS model, also dose-dependently inhibited the stress-induced increases in fecal output, but had no effect on naive, unstressed rats. This is the only demonstration to date that pregabalin can modulate stress-induced defecation in rats. A comparison of the effects in the two models suggests that pregabalin may be more potent at inhibiting the stress-induced increases in defecation than at inhibiting TNBS-induced colonic hypersensitivity.

The majority of studies of the effects of $\alpha_2\delta$ ligands on visceral pain have been restricted to acute models and largely to

those evoked by chemical irritants or pro-inflammatory stimuli. More recently investigators have studied the effects of gabapentin and pregabalin in models where less invasive and possibly more physiologically relevant stimuli have been used to evoke an acute or chronic phenotype. In a rat model, where repeated tonic colorectal distension induces hypersensitivity, oral pregabalin (10 and 30 mg/kg) inhibited the development of hyperalgesia (Million et al., 2007). Moreover, using Fos staining to indicate neuronal activation, a single oral dose of pregabalin (30 mg/kg) blunted the activation of lumbosacral spinal neurones. These data raise the possibility that in this model, pregabalin inhibits spinal sensitization and so inhibits the development of hyperalgesia. It has been demonstrated that maternal separation of rats in the early neonatal period, a presumably highly stressful stimulus, can give rise to hyperalgesia, revealed by colorectal distension, that is sustained for many weeks after the original stress (Coutinho et al., 2002). In an elegant study, to date only published as an abstract, Coelho et al. (2008) confirmed that a dose of gabapentin (30 mg/kg s.c.) that inhibited acute visceral pain evoked by intraperitoneal acetic acid, was also able to inhibit the pain behaviors evoked by colorectal distension in rats that had undergone maternal separation 9–11 weeks earlier.

New $\alpha_2\delta$ ligands are starting to appear in literature, but to date, only one of these, PD-217014, which has similar binding affinity at the $\alpha_2\delta$ binding site as pregabalin, has been investigated in an animal model of visceral hypersensitivity (Ohashi et al., 2008). In the TNBS model described previously, oral dosing of PD-217014 (3–100 mg/kg) dose-dependently inhibited the reduction in colonic nociception threshold observed 7 days after TNBS administration. Maximum inhibition was reached at 60 mg/kg and the inhibition at this dose was long lasting, reaching a peak at 2 h post-dose and lasting for between 6 and 8 h. Pharmacokinetic/pharmacodynamic (PK/PD) analysis clearly demonstrated that maximum anti-hyperalgesia coincided with peak plasma exposures. Interestingly, whilst the anti-hyperalgesic effect persisted at 6 h post-dose, plasma levels had at this time diminished to low levels. These observations suggest that the persistence of the pharmacological effect of PD-217014 is not simply related to plasma exposure and this phenomenon requires further investigation.

In a recent study, Ravnefjord et al. (2008) demonstrated in normal, unsensitized rats that pregabalin (10–200 μ mol/kg p.o.) inhibited the viscerosomatic response to phasic, noxious colorectal distension at 80 mmHg as well as the viscerosomatic response to ascending (10–80 mmHg), phasic distension. In this study, the highest dose of 200 μ mol/kg p.o. also inhibited the increases in cardiovascular parameters (blood pressure and heart rate) seen in response to noxious distension at 80 mmHg. However, one of the most interesting observations in this study, and one that reveals another potential mechanism of action of pregabalin to reduce pain thresholds in these distension models, was an apparent leftward shift in the colonic pressure-volume relationship. These observations suggest that pregabalin may increase the compliance of the colon in response to distension and by this mechanism could effectively reduce the intensity of the nociceptive stimulus. Similarly, this could be a mechanistic explanation for the observations of antinociceptive activity in models employing colorectal distension as a nociceptive stimulus.

CLINICAL EVIDENCE AND POTENTIAL UTILITY IN IBS

To date only two clinical studies have been published (Lee et al., 2005; Houghton et al., 2007) assessing the effect of these compounds on visceral sensitivity in IBS and one abstract in healthy volunteers (Chua et al., 2009). No results from clinical trials examining the efficacy of $\alpha_2\delta$ ligands on symptoms in IBS patients have yet appeared in literature. However, there is one investigator-sponsored small placebo-controlled trial of pregabalin in IBS (NCT00977197), another investigator sponsored study looking at the effect of pregabalin on colonic sensorimotor function in healthy volunteers (NCT01094808) and a company-sponsored clinical trial assessing the effect of the new generation $\alpha_2\delta$ ligand, PD-217014 in IBS (NCT00139672) currently listed on the US National Institute of Health ClinicalTrials.gov website.

The first study published assessed the effect of gabapentin (300 mg/day for the first 3 days and the 600 mg/day for the subsequent 2 days) on rectal sensitivity to balloon distension in IBS patients with diarrhea diagnosed using Rome II (IBS-D; Lee et al., 2005). The authors reported that the threshold pressures for bloating, discomfort and pain, and rectal compliance all significantly increased after gabapentin but not following placebo. The increase in rectal tone seen after meal ingestion was unaffected. Unfortunately however, no direct comparison was made with placebo in this study, so the significance of their gabapentin findings needs to be viewed with caution. The second study published by the authors assessed the effect of pregabalin (titrated from 50 mg tid to 200 mg tid over 3 weeks) in IBS patients who exhibited rectal hypersensitivity to mechanical distension (Houghton et al., 2007). In comparison to placebo, pregabalin was shown to significantly increase or normalize the sensory thresholds for pain (anti-allodynic effect), along with first sensation and desire to defecate (anti-hyperalgesic effect), without desensitizing (i.e., make hyposensitive) the perception of distension. If confirmed by larger studies and the results from the study currently in progress assessing the effect of pregabalin on colonic sensorimotor function in healthy volunteers (NCT01094808) proves to be negative, then this would suggest that as shown in the animal models, desensitization only occurs in the presence of an hypersensitive state. Such a compound would be most desirable for treatment of IBS and confirms studies in healthy volunteers showing that gabapentin reduces signs of central sensitization induced by intradermal capsaicin (i.e., the area of brush and pinprick hyperalgesia) but not spontaneous or evoked pain induced by capsaicin (Gottrup et al., 2004). Similarly, a more recent study only published in abstract form to date, showed that pregabalin prevents the development of secondary hyperalgesia in the proximal esophagus after distal esophageal acidification but had no effect on the primary hyperalgesia induced in the distal esophagus (Chua et al., 2009), supporting a central mode of action for pregabalin in reduction of pain.

In addition to pregabalin's effect on visceral sensation, and as with the gabapentin rectal motor-sensory study (Lee et al., 2005) and in the animal models (Ravnefjord et al., 2008) described previously, rectal compliance increased following pregabalin, although there appeared to be no association with the observed reduction in visceral pain (Houghton et al., 2007). This suggests additional mechanisms of action, as yet to be explored. Similar observations

have been seen before with both clonidine and nitroglycerine both increasing gastric compliance but only clonidine reducing pain perception (Thumshirn et al., 1999).

Generalized anxiety disorder, as with IBS, is a common disorder. Furthermore studies have shown that 32–58% of patients with IBS meet the diagnostic criteria for GAD (Lydiard, 2001), a condition which has recently been shown to improve following treatment with pregabalin (Stein et al., 2009). As well as improving overall anxiety levels in GAD patients, the study showed that treatment with pregabalin also led to an improvement in GI symptoms that very often coexist in these patients and similar to those seen in functional GI disorders, such as IBS (Stein et al., 2009). This raises the possibility that GI symptoms might improve as a consequence of the treatment of anxiety by pregabalin. Neither the presence of GAD nor levels of co-existing anxiety or depression were measured in the study of rectal hypersensitivity (Houghton et al., 2007), but the observation that pregabalin increased the sensory thresholds for first sensation and the desire to defecate, sensations not normally expected to be under significant psychological influence, might suggest that the anxiolytic properties of pregabalin were not playing a major role in modulating visceral sensation. In support of this hypothesis, other studies using anxiolytic agents, such as buspirone or antidepressants such as amitriptyline have shown no effect on colonic sensitivity to balloon distension (Mertz et al., 1998; Chial et al., 2003; Morgan et al., 2005). However, these observations do not exclude the possibility an anxiolytic effect for pregabalin in amelioration of IBS symptoms, especially in patients with anxiety-induced increased defecation (as implicated by the acute restraint stress animal model; Ohashi-Doi et al., 2010), but clinical trials are required in which psychological symptoms along with the cardinal IBS symptoms are measured to address the true efficacy of these agents in the treatment of IBS.

Other factors that might influence rectal sensation are the adverse effects associated with pregabalin, namely dizziness and/or somnolence. However, in the study of Houghton et al. (2007) these side effects had resolved in the majority of patients by the time sensitivity was assessed, and the change in sensory threshold in these patients was no different from that seen in those still retaining mild/moderate side effects, supporting data from animal studies (Ohashi-Doi et al., 2010).

Furthermore the improvement in sensory threshold tended to associate with a reduction in abdominal pain (Houghton et al., 2007), supporting the observations that pregabalin improves GI symptoms associated with GAD (Stein et al., 2009), and pain in patients with fibromyalgia (Hauser et al., 2009; Smith and Barkin, 2010; Straube et al., 2010). The results from the ongoing clinical trials are eagerly awaited, and whether the patients have been appropriately phenotyped to identify any sub-group improvement based on their hypersensitivity or anxiety status also remains to be revealed.

CONCLUSION

Gabapentin and pregabalin are valuable medicines being used for the treatment of a number of conditions, including neuropathic pain, epilepsy, anxiety, and fibromyalgia. A body of evidence implicates binding to the $\alpha_2\delta$ subunits of voltage-gated calcium channels on presynaptic neuronal membranes as their most likely

mechanism of action. However, recent data also points at potential additional mechanisms within the cell which may underwrite some of their chronic effects and also indicates potential modulation of pro-inflammatory pathways through inhibition of NF- κ B signaling. The modulation of calcium fluxes evoked by gabapentin and pregabalin has been shown to reduce the release of a broad range of both excitatory and inhibitory neurotransmitters, primarily in the central nervous system and hence this mechanism has great potential to influence signaling pathways, including those involved in pain transmission. Emerging data supports a role for the $\alpha_2\delta$ subunit in neurotransmission in the enteric nervous system, but the functional importance of these observations has yet to be fully elucidated.

Data from animal models provides evidence for the inhibition of both visceral nociception and GI function by gabapentin and pregabalin in animals in which hypersensitivity has been induced by either an inflammatory stimulus or stress, but largely illustrates an absence of such activity on basal sensitivity or function.

When particularly strong noxious stimuli are used (acetic acid or distension to high pressures) effects on sensation in unsensitized animals can be observed. These observations are in concordance with earlier experiments performed using isolated *in vitro* preparations from animals in which hyperalgesia had been established. The precise mechanism through which the $\alpha_2\delta$ ligands inhibit

intestinal allodynia and hyperalgesia has only been hinted at and much remains as supposition. The extensive literature that indicates the reduction in the release of neurotransmitters at the spinal and supraspinal level by $\alpha_2\delta$ ligands remains a valid hypothesis to explain the observations, with some supporting data obtained from animal models of visceral pain.

The limited number of clinical studies of visceral pain performed and reported to date support the observations in animals. In patients with IBS, both gabapentin and pregabalin have been shown to reduce rectal sensitivity to balloon distension and in the study with pregabalin, anti-allodynia, and anti-hyperalgesia was demonstrated in subjects with pre-characterized rectal hypersensitivity. Data is expected soon from a similar study in healthy volunteers which will illustrate whether these agents have, like in many animal models, little effect on sensory thresholds in subjects without hypersensitivity. Both animal and clinical data also suggest that $\alpha_2\delta$ ligands may alter intestinal compliance and the significance of this needs further investigation. These data, supported by observations from animal studies, support further investigation of $\alpha_2\delta$ ligands in disorders characterized by visceral hypersensitivity such as IBS. Carefully controlled, randomized clinical trials will be needed to fully understand the potential of these agents to treat these bothersome conditions.

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